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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,266	05/16/2008	Reiko Matsuyama	MATSUYAMA1	1891

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Browdy and Neimark, PLLC
1625 K Street, N.W.
Suite 1100
Washington, DC 20006

EXAMINER	
TSAY, MARSHA M	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,266	MATSUYAMA ET AL.	
	Examiner	Art Unit	
	Marsha Tsay	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *23-43* is/are pending in the application.

5a) Of the above claim(s) *37-43* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *23-36* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *30 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/05/11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to Applicants' remarks received July 5, 2011.

Applicants' arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous Office actions are hereby withdrawn.

Claims 1-22 are canceled. Claims 37-43 are withdrawn. Claims 23-36, to the species chicken β-actin promoter, dhfr gene, CHO cells, are currently under examination.

Priority: The request for priority to JAPAN 2004-096215, filed March 29, 2004, and JAPAN 2003-282033, filed July 29, 1993, is acknowledged. Applicants' request to retrieve the priority applications of July 5, 2011 is acknowledged. Certified copies of the foreign priority documents have been placed in the file on September 6, 2011.

Objections and Rejections

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32-34 are dependent on claim 23, which recites "and/or" language regarding the α chain, the αE chain, the γ chain and the γ' chain. It is unclear how claims 32-34 further limits claim 23 since as currently amended, claim 23 already recites incorporating into the animal cell,

one or both of a gene encoding an α chain and a gene encoding an αE chain, and one or both of a gene encoding a γ chain and a gene encoding a γ' chain. Further clarification is requested.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23-24, 29, 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roy et al. (1991 Journal of Biological Chemistry 266(8): 4758-4763; previously cited) (Roy et al. '91) in view of Roy et al. (1994 Journal of Biological Chemistry 269(1): 691-695) (Roy et al. '94). For examination purposes, claim 23 has been interpreted as: a process for preparing a recombinant fibrinogen-producing cell which produces a high level of recombinant fibrinogen of 100 μg/mL or more, wherein said process comprises incorporating into an animal cell, genes encoding an α chain and/or an αE variant thereof, a β chain, and a γ chain and/or a γ' variant thereof, where said animal cell is capable of producing a high level of fibrinogen of 100 μg/mL or more. MPEP 2106 states that language that suggests or makes optional but does not require steps to be performed or does not limit a claim to a particular structure does not limit the scope of a claim or claim limitation.

Roy et al. '91 disclose a method of making a recombinant fibrinogen producing cell which expresses fibrinogen protein comprising transfecting COS-1 cells with either pRSVNeo-Bβ, pRSVNeo-Aα, or pRSVNeo-γ or with combinations of equal amounts of two of these

expression vectors, or with equal amounts of all three expression vectors (p. 4759). Roy et al. '91 do not teach unequal amounts of pRSVNeo-Bβ, pRSVNeo-Aα, or pRSVNeo-γ.

Roy et al. '94 disclose that increased expression of any fibrinogen, elicited by transfection with vectors containing individual fibrinogen chain cDNAs, specifically up-regulates the expression of the other two chains (p. 695). Roy et al. '94 further disclose that transcription of the three fibrinogen chains is tightly linked and increased expression of any chain specifically leads to increased synthesis of the other two chains (p. 691). Therefore, Roy et al. '94 suggest that unequal amounts of α, β, and γ genes increases the expression of fibrinogen.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Roy et al. '91 by preparing a recombinant fibrinogen-producing cell that produces a high level of recombinant fibrinogen by transfecting COS-1 cells with combinations of pRSVNeo-Bβ, pRSVNeo-Aα, and pRSVNeo-γ such that one expression vector is in a greater amount (i.e. pRSVNeo-γ) rather than with equal amounts said expression vectors since Roy et al. '94 disclose that the transcription of the three fibrinogen chains is tightly linked and increased expression of any chain specifically leads to increased synthesis of the other two chains (claims 23-24, 29, 32-34). The motivation to do is given by Roy et al. '94, which disclose that increasing the expression of one fibrinogen chain up-regulates the expression of the other two chains. Further, since there are only three chains (i.e. α, β, and γ), it would be reasonable for one of ordinary skill to determine the ratio and which chain should be increased relative to the other two chains in order to arrive at the optimum ratio that produces the most fibrinogen.

Further, MPEP 2143 states that that the rationale to support a conclusion that the claim would have been obvious is that a particular known technique was recognized as part of the ordinary capabilities of one skilled in the art. One of ordinary skill in the art would have been capable of applying this known technique to a known product and the results would have been predictable to one of ordinary skill in the art.

Regarding the "high level of fibrinogen of 100 μg/mL or more", as noted above, MPEP 2106 states that language that suggests or makes optional but does not require steps to be performed or does not limit a claim to a particular structure does not limit the scope of a claim or claim limitation, i.e. a cell that is capable of producing a high level of fibrinogen of 100 μg/ml does not mean that it actually produces a high level of fibrinogen of 100 μg/ml.

In their remarks, Applicants assert that **(1)** the only disclosure in the cited and applied Roy reference of preparing cells that can produce all three of the α, β, and γ of fibrinogen is when equal amounts of all three expression vectors, each expressing a different chain, were used to transfect COS-1 cells to obtain a stable cell line (see page 4759, right column, second paragraph of the section entitled "Transfection and Selection of Stable Cell Lines"). There is no teaching whatsoever in Roy that would lead one of ordinary skill in the art to use unequal amounts of the genes encoding the three chains, much less specifically the unequal amounts in a ratio of (α+β):γ of 1:1 to 1:3, as positively recited in the present claims. See also the present specification near the bottom of page ii, where the specific ratios of the genes for the individual chains, i.e., (α+β):γ of 1:1:2 to 1:1:6 (which is the same as a ratio of (α+β):γ of 1:1 to 1:3). Thus, Roy's disclosures and teachings simply cannot lead one of ordinary skill in the art to arrive at the

presently claimed invention where a high level of fibrinogen (100 μg/ml or more) is capable of being produced in the recombinant fibrinogen-producing cell. Note that in the "Quantitation of Secreted Fibrinogen" section in the left column on page 4760 of Roy, the concentration range of the standard curve using pure human fibrinogen is from 0.25-4.0 μg/ml and it stands to reason that this is the concentration range measured for fibrinogen secreted into the culture media from the COS-α, β, γ cells. This appears to be confirmed by the disclosure in the last sentence of the Results in the left column on page 4762 of Roy that an average of 2.08 μg of fibrinogen was secreted in 24 hrs. The production level of at least 100 μg/ml that the cells prepared by the presently claimed method are capable of producing is far above the production level taught in Roy. It would certainly not have been obvious and predictable to one of ordinary skill in the art that unequal numbers of genes for the α, β, γ chains, as specified in the presently amended claims, would cause the cells to produce such a high level of fibrinogen.

Applicant's arguments have been fully considered but they are not persuasive.

(1) Reply: The deficiency of the Roy reference to disclose an unequal amount of the α, β, γ chains is believed to be remedied by the newly cited Roy et al. '94 reference.

Regarding Applicants' remarks that the production level of at least 100 μg/ml that the cells prepared by the presently claimed method are capable of producing is far above the production level taught in Roy, as noted in the 103(a) rejection above, MPEP 2106 states that language that suggests or makes optional but does not require steps to be performed or does not limit a claim to a particular structure does not limit the scope of a claim or claim limitation, i.e. a cell that is *capable of* producing a high level of fibrinogen of 100 μg/ml does not mean that it actually produces a high level of fibrinogen of 100 μg/ml.

Further, since the newly cited Roy et al. '94 reference discloses increasing the expression of any chain specifically leads to increased synthesis of the other two chains, one of ordinary skill would reasonably expect that the cell prepared by the method of Roy et al. '94 would have a high level of fibrinogen that is within the instant concentration.

For at least these reasons, the claims remain rejected under 35 U.S.C. 103(a).

Claims 25-26, 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roy et al. (1991 Journal of Biological Chemistry 266(8): 4758-4763; previously cited) (Roy et al. '91) in view of Roy et al. (1994 Journal of Biological Chemistry 269(1): 691-695) (Roy et al. '94) in view of Lord et al. (1993 Blood Coagulation and Fibrinolysis 4(1): 55, abstract only; previously cited). The teachings of Roy et al. '91 in view of Roy et al. '94 are outlined above. Roy et al. '91 in view of Roy et al. '94 do not teach that an expression vector encodes for more than one fibrinogen chain.

Lord et al. disclose that fibrinogen chains can be individually cloned into the same expression vector (abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teachings of Roy et al. '91 in view of Roy et al. '94 by cloning in combinations of two or three of the fibrinogen chains (selected from the α chain, the β chain, and the γ chain), into the same expression vector as suggested by Lord et al. and transfecting the animal cell with the combination of expression vectors such that the transfected animal cell has an unequal

amount of α chain, β chain, and γ chain genes present in said cell, i.e. a greater concentration of γ chain genes (claims 25-26, 28). The motivation to do is given by Lord et al. which disclose that genes encoding fibrinogen chains can be cloned into the same expression vector; therefore, it would be reasonable for one of ordinary skill to determine which combination of vectors and fibrinogen genes would produce a high concentration of fibrinogen protein.

Reply: The deficiency of Roy et al. '91 to disclose an unequal amount of the α, β, γ chains is believed to be remedied by the newly cited Roy et al. '94 reference. See also the reply of (1) above.

Claims 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roy et al. (1991 Journal of Biological Chemistry 266(8): 4758-4763; previously cited) (Roy et al. '91) in view of Roy et al. (1994 Journal of Biological Chemistry 269(1): 691-695) (Roy et al. '94) in view of Lord (US 6037457; previously cited). The teachings of Roy et al. '91 in view of Roy et al. '94 are outlined above. Roy et al. '91 in view of Roy et al. '94 do not teach CHO cells.

Lord discloses that recombinant fibrinogen can be expressed using CHO cells (col. 9-10).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Roy et al. '91 in view of Roy et al. '94 by substituting the CHO cells of Lord for the COS-1 cells used in Roy et al. '91 (claim 35). The motivation to do so is given by Lord, which discloses that CHO cells, COS-1, HepG2 are all animal cells that can be used to successfully express recombinant fibrinogen. Regarding claim 36, it should be noted that it would be well within the skill and knowledge of one of ordinary skill to determine which

specific strain of CHO cells will express a high concentration of fibrinogen protein compared to other strains since different mammalian expression systems are known in the art. The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine which mammalian expression system will express a high concentration of fibrinogen protein. See also MPEP 2144.04-2144.05.

Reply: The deficiency of Roy et al. '91 to disclose an unequal amount of the α, β, γ chains is believed to be remedied by the newly cited Roy et al. '94 reference. See also the reply of (1) above.

Claims 27, 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roy et al. (1991 Journal of Biological Chemistry 266(8): 4758-4763; previously cited) (Roy et al. '91) in view of Roy et al. (1994 Journal of Biological Chemistry 269(1): 691-695) (Roy et al. '94) in view of Lord (US 6037457; previously cited) in view of Estes et al. (US 7423135; previously cited). The teachings of Roy et al. '91 in view of Roy et al. '94 in view of Lord are outlined above. Roy et al. '91 in view of Roy et al. '94 in view of Lord do not teach chicken β-actin promoter and a dhfr gene.

Estes et al. disclose that chicken β-actin promoter can be employed with a dhfr gene in a suitable expression system for CHO cells (col. 7-11).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teachings of Roy et al. '91 in view of Roy et al. '94 in view of Lord by substituting the chicken β-actin promoter and the dhfr gene of Estes et al. for the SV40 promoter used in Roy

et al. (claims 30-31). The motivation to do so is given by Estes et al., which disclose that chicken β-actin promoters are known in the art and can be used with the dhfr gene in a suitable expression system. Further, regarding claim 27, the cited art disclose a combination of the α, β, γ, and neo and dhfr genes. It would be reasonable for one of ordinary skill to determine which combination of promoters and genes can be used with an animal cell to express a high concentration of fibrinogen protein. The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine which mammalian expression system will express a high concentration of fibrinogen protein. See also MPEP 2144.04-2144.05.

Reply: The deficiency of Roy et al. '91 to disclose an unequal amount of the α, β, γ chains is believed to be remedied by the newly cited Roy et al. '94 reference. See also the reply of (1) above.

Applicants' remarks and amendments regarding withdrawn claim 37 and the restriction requirement will be considered when the elected claims are in condition for allowance.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha Tsay whose telephone number is (571)272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm E.T.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

September 9, 2011

M. Tsay
Art Unit 1656

/Manjunath N. Rao /
Supervisory Patent Examiner, Art Unit 1656